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Robert M. Moriarty

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19. ABSTRACT (Continue on reverse if necessary and identify by block number)

During the past year, (+) 3-oximinotropan-2-one methiodide has been synthesized as well as the racemic compound (±) 3-oximinotropan-2-one. The regioisomeric (±)2-oximino-tropan-3-one has been prepared and the corresponding hydrochloride has also been synthesized. Binding constants to AChE, pKa's and reactivation activities for these compound have been determined. Several oximes and a-ketones in the phencyclidine series have also been synthesized and submitted for testing. Among azabicyclooctane derivatives, 2,4-bisoximino tropan-3-one methiodide, 2,4-dimethoxy-3-oximinotropane methiodide and 2-carbomethoxy-3-oximinotropane methiodide have been synthesized and submitted for testing. 1-Methyl-3-oximino-5,5-diphenyl azacycloheptan-4-one methiodide has also been synthesized and submitted. A novel type of atropine-like molecule has been made, namely,3-acetophenyl tropine oxime hydrochloride. Four novel potential antimalarials have been synthesized, namely, 2-(methoxymethyl carbonyl)pyridine thiosemicarbazone, 2-(methoxymethylcarbonyl)pyridine 4'-phenylthiosemi-carbazone, 2,6-bis(methoxymethylcarbonyl)pyridine bis-thiosemicarbazone and 2,6-bis(methoxy-methylcarbonyl)pyridine bis-4'-phenylthiosemicarbazone and these compounds have been submitted for testing.

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BRIDGED BICYCLIC SYSTEMS AND PRETREATMENT DRUGS AS ACETYLCHOLINESTERASE REACTIVATORS

Annual Report
July 15, 1985 through July 14, 1986

Robert M. Moriarty

November 15, 1989

Supported by
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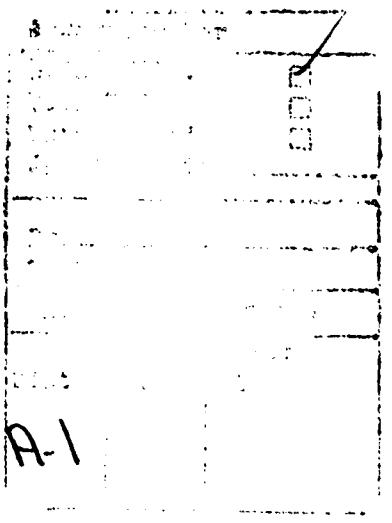
University of Illinois at Chicago
Department of Chemistry
P.O. Box 4348
Chicago, Illinois 60680



1. SUMMARY

During the past year, (+) 3-oximinotropan-2-one methiodide has been synthesized as well as the racemic compound (±) 3-oximinotropan-2-one. The regioisomeric (±) 2-oximino-tropan-3 one has been prepared and the corresponding hydrochloride has also been synthesized. Binding constants to AChE, pKa's and reactivation activities for these compound have been determined. Several oximes and α-ketones in the phencyclidine series have also been synthesized and submitted for testing. Among azabicyclooctane derivatives, 2,4-bisoximino tropan 3 one methiodide, 2,4-dimethoxy-3-oximinotropane methiodide and 2-carbomethoxy-3-oximinotropane methiodide have been synthesized and submitted for testing. 1-Methyl-3-oximino-5,5 diphenyl azacycloheptan-4-one methiodide has also been synthesized and submitted. A novel type of atropine-like molecule has been made, namely,3-acetophenyl tropine oxime hydrochloride.

Four novel compounds have been synthesized, namely, 2-(methoxymethyl carbonyl)pyridine thiosemicarbazone, 2-(methoxymethylcarbonyl)pyridine 4'-phenylthiosemi-carbazone, 2,6-bis(methoxymethylcarbonyl)pyridine bis-thiosemicarbazone and 2,6-bis(methoxy-methylcarbonyl)pyridine bis-4'-phenylthiosemicarbazone and these compounds have been submitted for testing.

Test Results

Pyridine Thiosemicarbazones

Test results are not presently available on: OP-700, WR-254750, BL-09846; OP-688, WR-254749, BL-09837; OP-661, WR-2547489, BL-09828, OP-705, WR-254751, BL 09855.

Oxmino Tropanones

Analogs PRV-188, PRV-151, OP-735, and PRV-163 were less efficient as reactivators relative to 2-PAM.

2. FOREWORD

This work was supported by the U.S. Army Medical Research and Development Under Contract No. DAMD17-85-C-5190.

The Principal Investigator thanks Om Prakash, Ph.D., Pushpa R Vavilikolanu and Payman Farid for synthetic work and DianA E. Clarisse for kinetic measurements. Thomas Dougherty also assisted in kinetic determinations and analysis. Invaluable suggestions and guidance in this project were given by H. A. Musallam and R. Engle of USAMRDC.

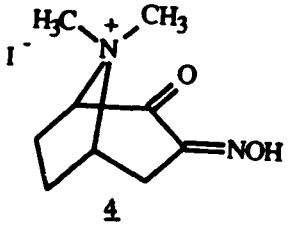
TABLE OF CONTENTS

3. BACKGROUND

The central goal of the research carried out during this year has been the synthesis of bridged bicyclic compounds that are structurally related to acetylcholine, modified to incorporate a nucleophilic oximino function that could potentialyy reactivate phosphorylated acetylcholinesterase. It has been amply demonstrated that certain classes of compounds possess high affinity for acetylcholine receptors. By homology, structurally related oximes should show affinity for the active site of the enzyme. Of the known classes, this study concentrates on those related to atropine, that is, containing the [3.2.1] azabicyclooctane system and those related to phencyclidine. It has been our aim to increase the ability of tropan alkaloids to reactivate the enzyme by increasing the stability of the oximate anion encorporated within this basic system. This was done initially by placing an α-hydroxy function adjacent to the ketones. A more powerful stabilizing effect has been achieved using the α-keto group because of resonance stabilization of the α-keto oximate anion.

The following structural types fulfill these criteria: 4, 7e, 10, 17, 20, 26, 31, 35, 36, 40, 41 and 45 and these have been synthesized in the past year.

i) ***Reactivators***



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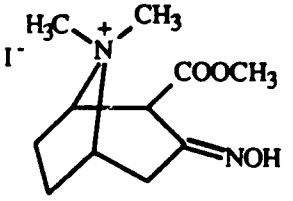
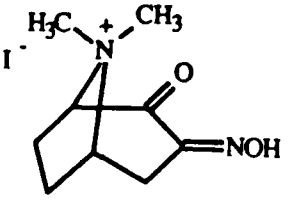


7e

2-Carbomethoxy-3-oximino tropane methiodide



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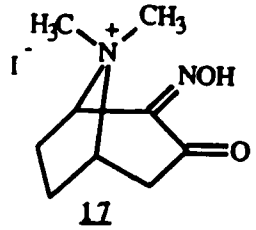
(±)-3-Oximino-tropan-2-one methiodide



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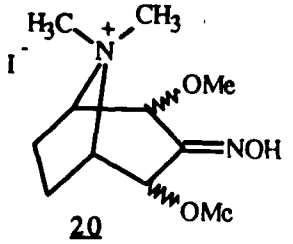
2-Oximino-tropan-3-one methiodide



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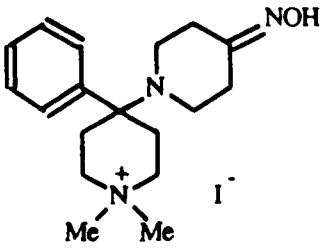
2,4-Dimethoxy-3-oximino-tropane methiodide



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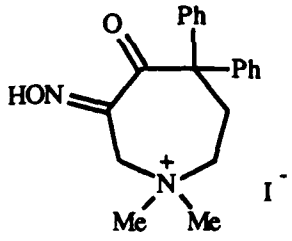
1-(1'-Dimethyl-4'-phenylpiperidinal) piperidoneoxime iodide



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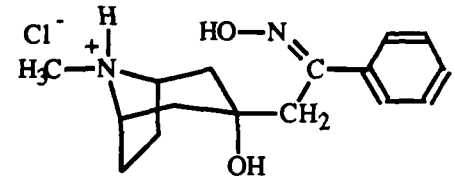
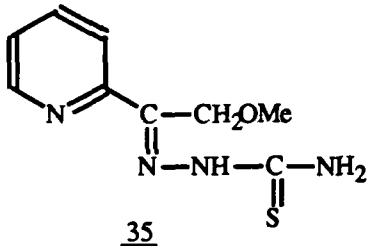
1-Methyl-3-oximino-5,5-diphenyl



45

3-Acetophenyl tropine oxime hydrochloride

ii) bis-Thiosemicarbazones of pyridine



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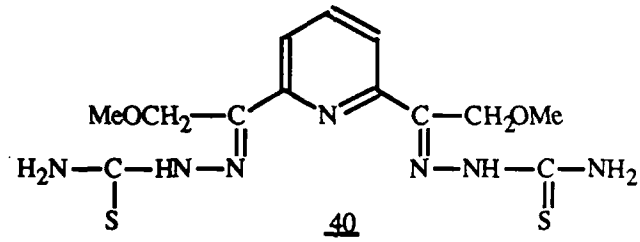
2-(Methoxymethylcarbonyl)
pyridine thiosemicarbazone



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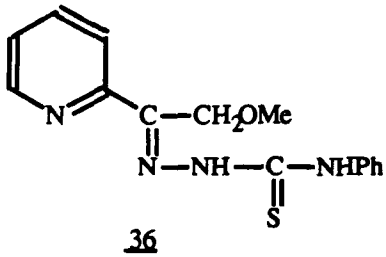
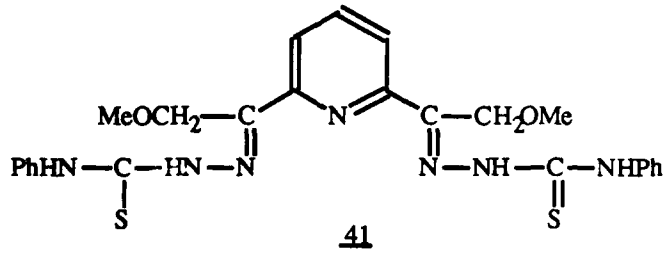
2,6-bis(Methoxymethylcarbonyl)
pyridine bis-thiosemicarbazone



36

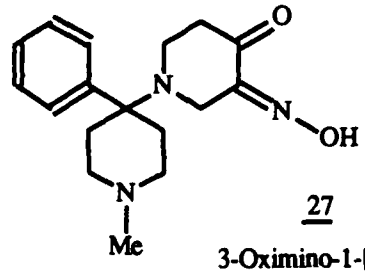
2-(Methoxymethylcarbonyl)
pyridine 4'-phenylthiosemicarbazone



41

2,6-bis(Methoxymethylcarbonyl)
pyridine bis-4'-phenylthiosemicarbazone

The following oxime has also been synthesized, and its quaternization is currently under study.



27

3-Oximino-1-[phenylpiperidinyl(1'-methyl)]piperidone-4-one

4. MAJOR ACCOMPLISHMENTS DURING THE YEAR

a. 3-Oximino-tropan-2-one methiodide has been synthesized in optically active and racemic forms.

b. 2-Oximino-tropan-3-one hydrochloride has been synthesized in its racemic form.

c. Several oximes of the phencyclidine family have been successfully prepared.

d. The oximino derivative of azacycloheptan-4-one has been synthesized.

e. Various mono as well as *bis*-thiosemicarbazones of pyridine have been synthesize

f. The synthesis of a new series of atropine analogues is underway. The parent compound has been made in large quantity and fully characterized.

g. Incorporation of the carbonyl functional group alpha to the oxime has increased the stability of the oximate anion. This is illustrated by a dimunition in pKa from 11 to 6.8 in the case of tropane system.

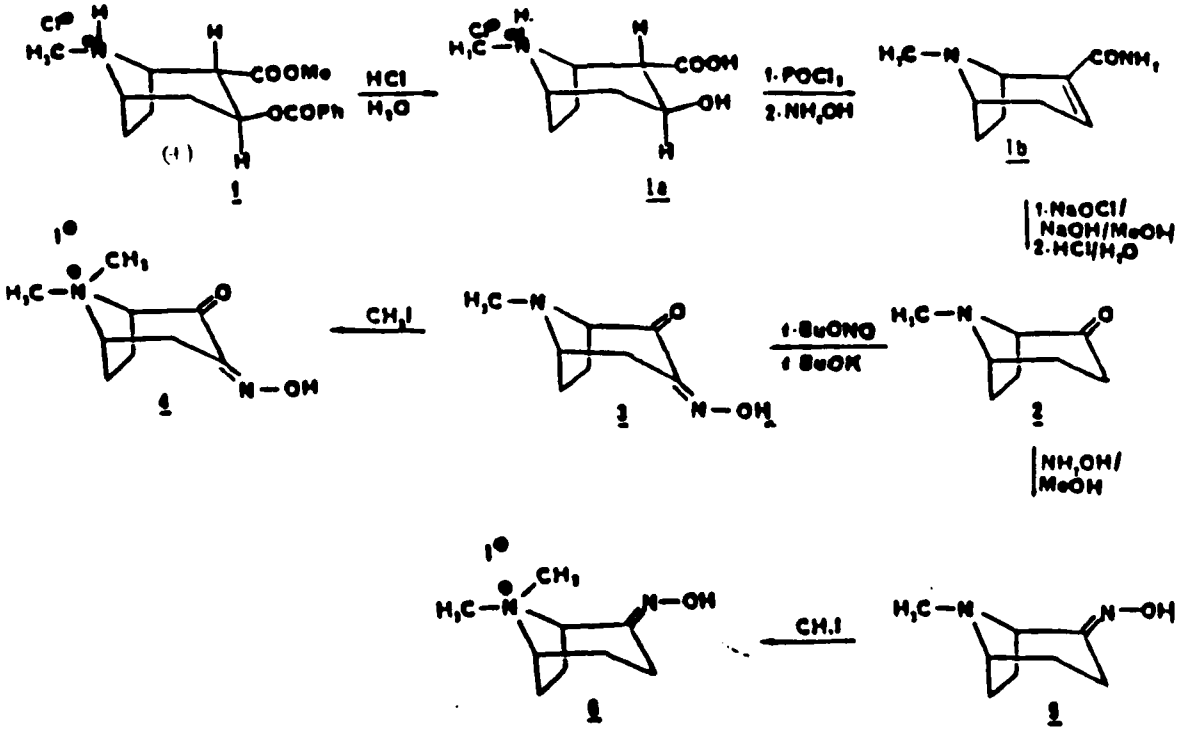
h. The pKa and binding constants of the structurally related pairs of compounds have been determined and compared.

i. It is now possible to gain insight into the stereospecificity of the active site for reactivators.

5. DISCUSSION OF SYNTHESES

i) Reactivators

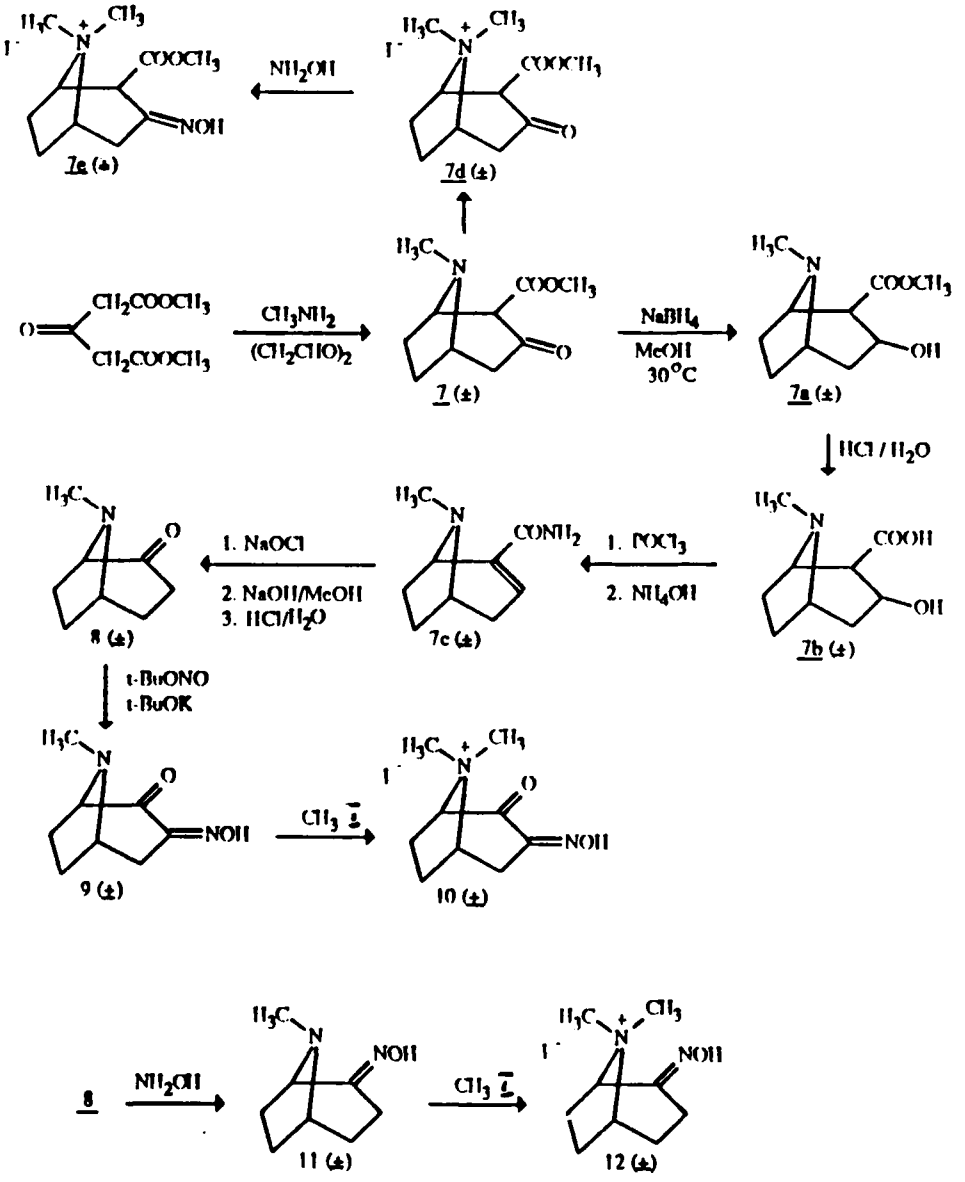
The synthesis of optically active tropan-2-one is based on the work of Bell and Archer (1960).[1] The scheme involves the systematic degradation of (+) l-cocaine hydrochloride 1. Hydrolysis of compound 1 with aqueous hydrochloric acid gives compound 1a, which on treatment with phosphorus oxychloride and then with ammonium hydroxide, gives the unsaturated carboxamide 1b. The optically ketone 2 was obtained from 1b by treatment with sodium hypochlorite in methanolic sodium hydroxide and then with aqueous hydrochloric acid. Reaction of the optically active ketone 2 with hydroxylamine in methanol afforded oxime 5. The methiodide of oxime 5 was prepared by treating oxime 5 with excess of methyl iodide in methylene chloride. The optically active ketone 2, on treatment with t-BuOK and t-BuONO, afforded α-keto oxime 3 which was converted into its methiodide 4 using methyl iodide in methylene chloride (Scheme 1).



Scheme 1

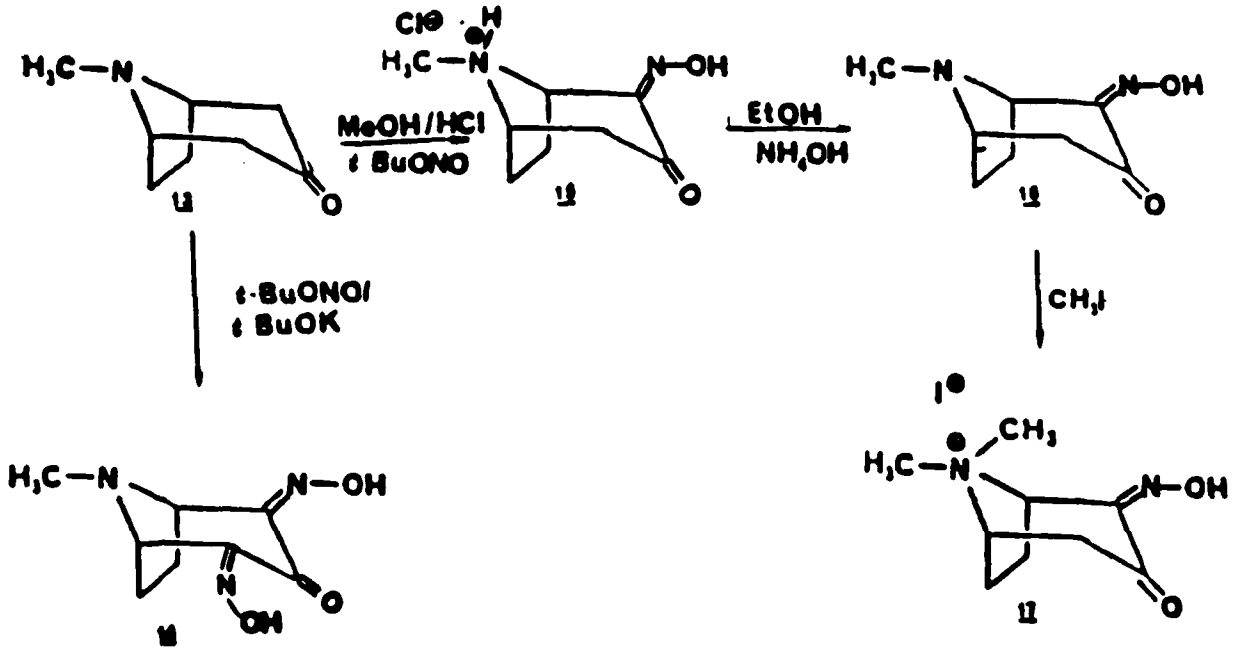
Next, racemic tropan-2-one was synthesized. The synthesis of racemic tropan-2-one depends On the total synthesis of 2-carbomethoxy tropan-3-one.[2] Of the methods outlined by Findlay, the modified Willstatter scheme proved superior in terms of yield as well as cost. The racemic ketone 8 was obtained using some modification of the method of Bell and Archer (Scheme 2).[3,4] 2-Carbomethoxytropan-one (7) was synthesized by the reaction of β-ketoglutarate monomethyl ester with methylamine and succinaldehyde. Reduction of compound 7 with sodium borohydride in methanol at -30°C afforded the corresponding 2-carbomethoxy tropan-3-ol (7a). Hydrochloride 7b was obtained by treating compound 7a with hydrochloric acid. Dehydration of compound 7b with

phosphorus oxychloride and then treatment with ammonium hydroxide afforded the carboxamide 7c. Carboxamide 7c was converted to racemic tropan-2-one 8 by treating it with sodium hypochlorite in methanolic sodium hydroxide and then with aqueous hydrochloric acid. In this way tropan-2-one was obtained from 2-carbomethoxytropan-3-one. Racemic ketone 8 was converted to its oxime 11 by reacting it with hydroxylamine in methanol, then 11 was converted to α-keto oxime 9 by treatment with t-BuOK and t-BuONO and then it was converted to the methiodide 10 by treatment with methyl iodide. Ketone 7 was also converted first to the methiodide 7d by treating it with methyl iodide and then finally to the oxime methiodide 7e by treatment with hydroxylamine (Scheme 2).



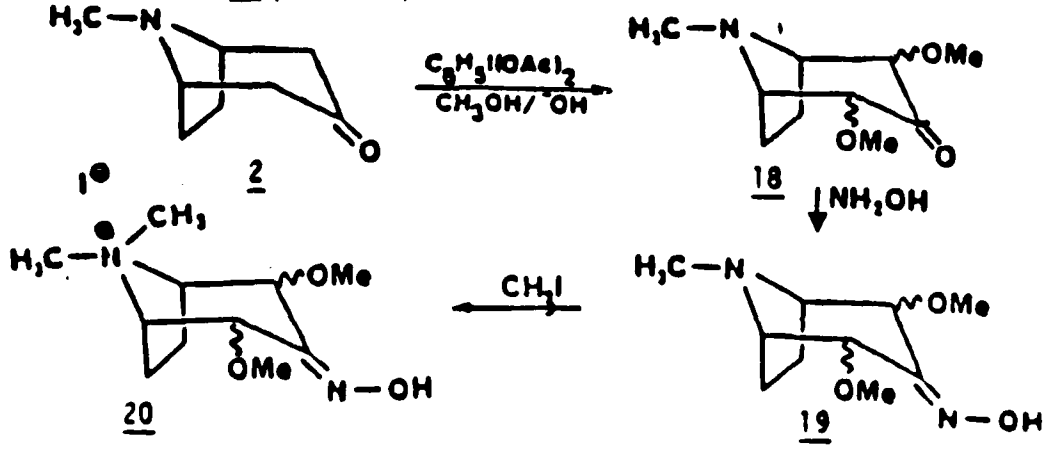
Scheme 2

The nitrosation reaction conditions of t-BuOK/t-BuONO, however, used on tropan-3-one (13) gave the bisoxime 14 (Scheme 3). This is reasonable since there are 2 equivalent α-positions and an excess of both t-BuONO and t-BuOK is used. Varying the quantities of nitrosating agent and base gave not the simple α-keto oxime but a lower yield of bisoxime. Finally after several trials, mono oxime 15 was successfully prepared from tropane-3-one by treating it with t-BuONO in methanolic hydrochloric acid.[5,6] Free base (15) was obtained by treating 15 with 14 ammonium hydroxide in ethanol. Quaternization of 15 with methyl iodide in methylene chloride afforded methiodide 17 (Scheme 3). In this manner, the effect of positional isomerism as well as stereochemistry may be determined.



Scheme 3

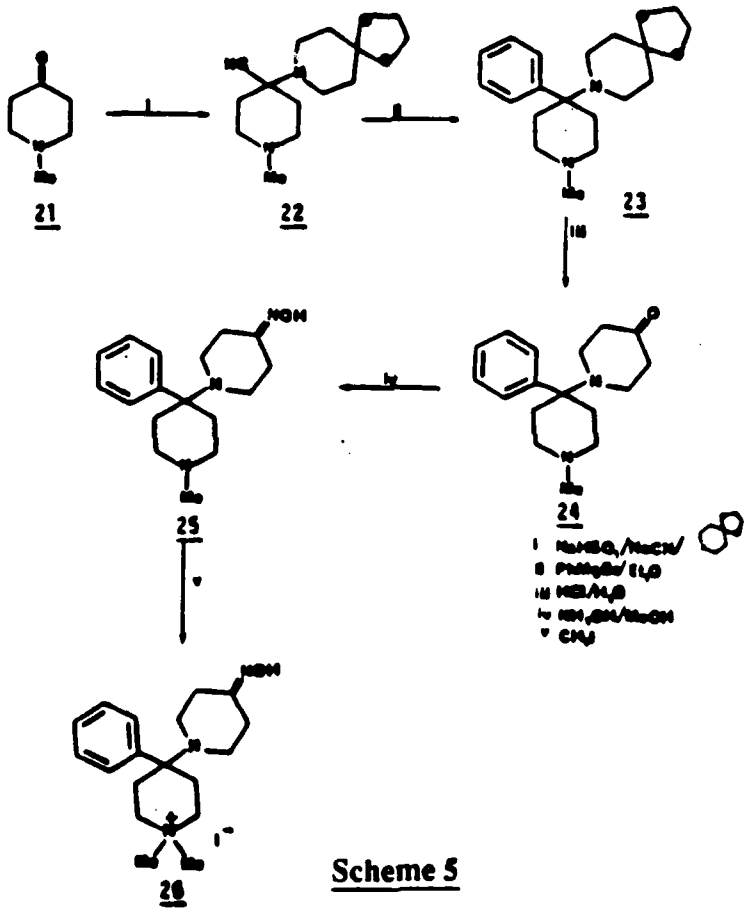
Tropan-3-one (2) was converted to 2,4-dimethoxytropan-3-one (18) by treating it with iodosobenzene diacetate in methanolic potassium hydroxide.[7] Dimethoxy compound 18 was converted to oxime 19 by treating it with hydroxylamine. Treatment of oxime 19 with methyl iodide afforded methiodide 20 (Scheme 4).



Scheme 4

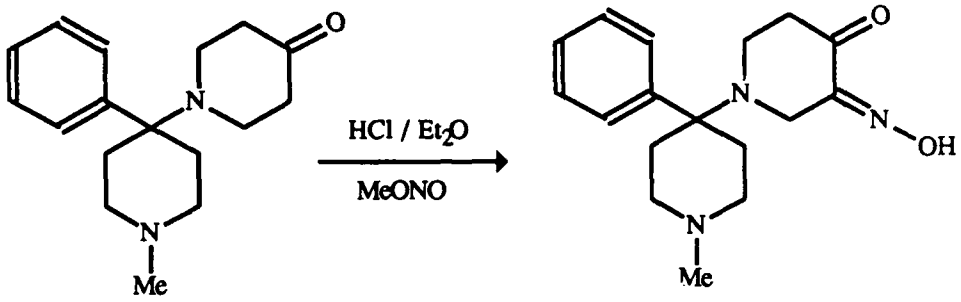
The next series of compounds is exemplified by the synthesis of 1-(1',1'dimethyl-4-phenylpiperidinyl)piperidone oxime iodide (26). Essentially, the Bruylants synthesis[7] of phencyclidines was followed with the essential difference being in the protected ketone which is unmasked at the final stages.[8] This modification results in radically improved yields.

The phencyclidine ketone 24 was obtained from N-methylpiperidone (21) by treating it first with sodium cyanide and then with sodium bisulfite and finally with phenlmagnesium bromide. After hydrolysis of 23, ketone 24 was obtained, which was converted to its oxime 25 by reaction in methanol with bydroxylamine. Quaternization of the oxime 25 with methyl iodide gave only the mono methiodide (26) since the nitrogen at the juncture of the three rings is sterically hindered (Scheme 5).



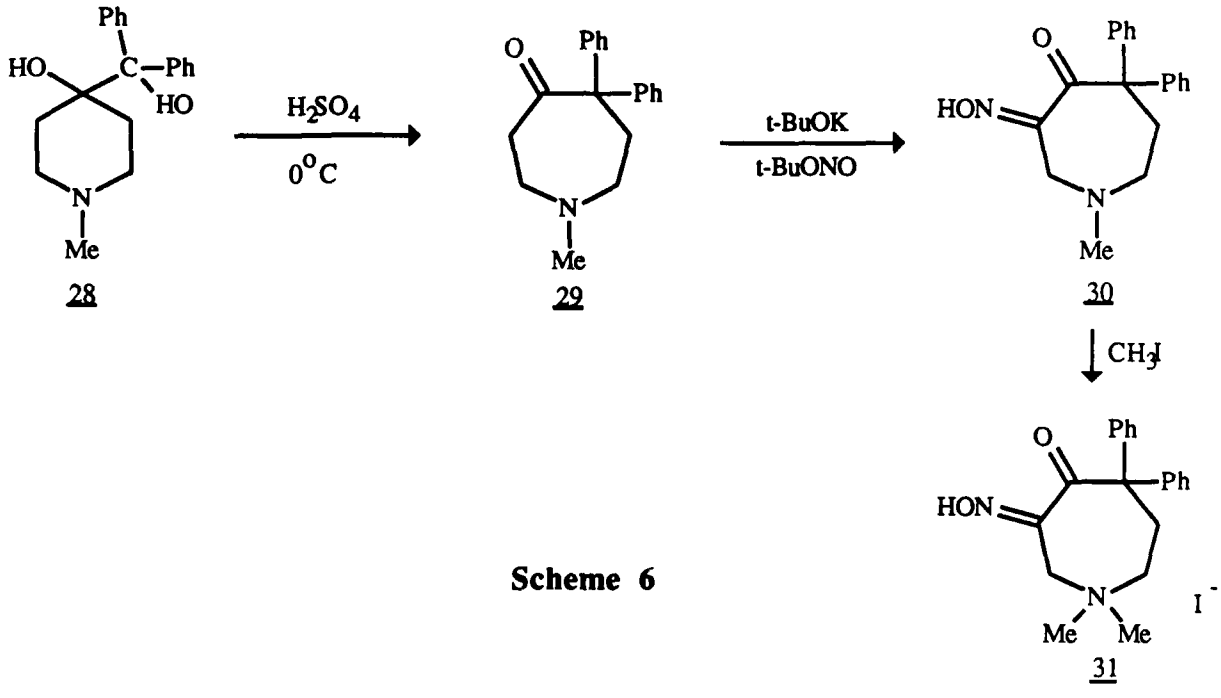
Scheme 5

The application of nitrosation to the phencyclidine oximes has proved promising and is at present being standardized.



24 27

Next, we synthesized azacycloheptanone oxime. The azacycloheptan-4-one (29)[9] was obtained from piperidino derivative 28 by the treatment with sulfuric acid at 0°C. α-ketoxime of azacycloheptan-4-one (30) was obtained by treating ketone 29, with t-BuOK and t-BuONO. Finally, it was converted to methiodide (31) by treating it with methyl iodide (Scheme 6).

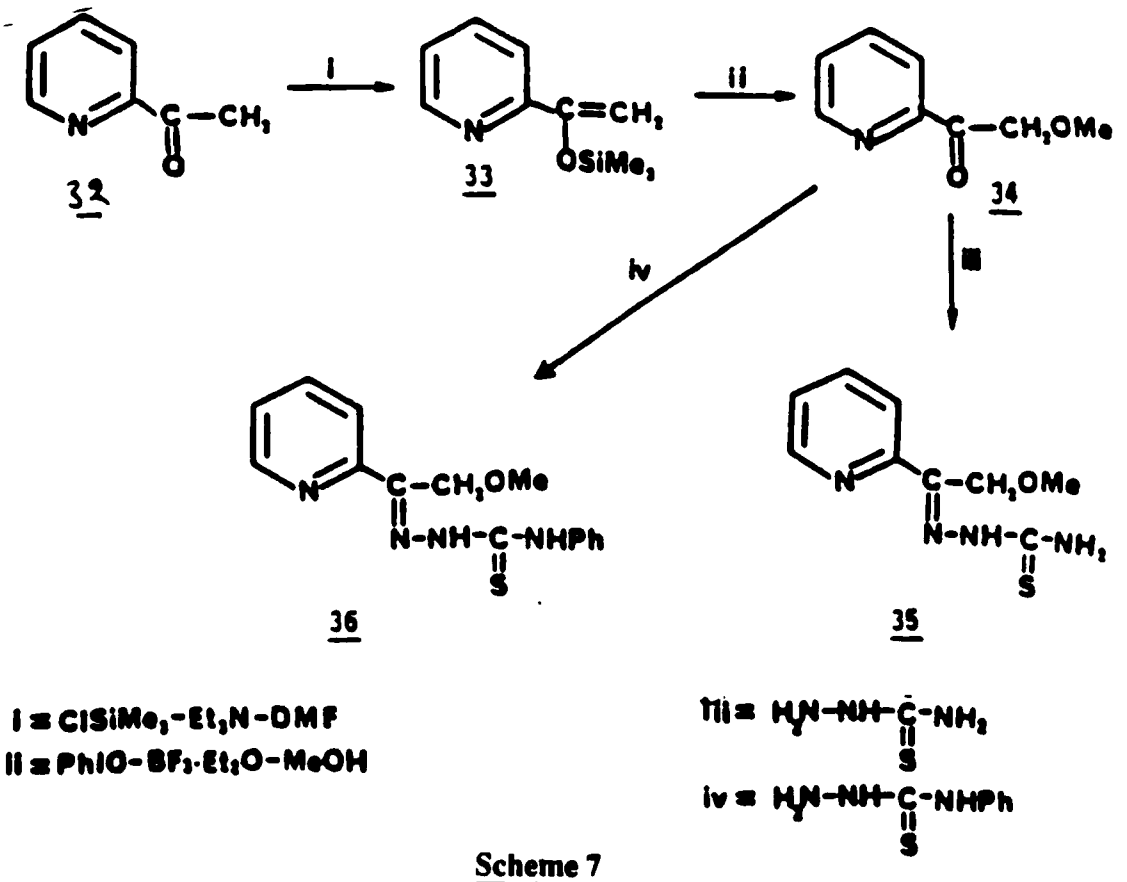


28 29 30 31

Scheme 6

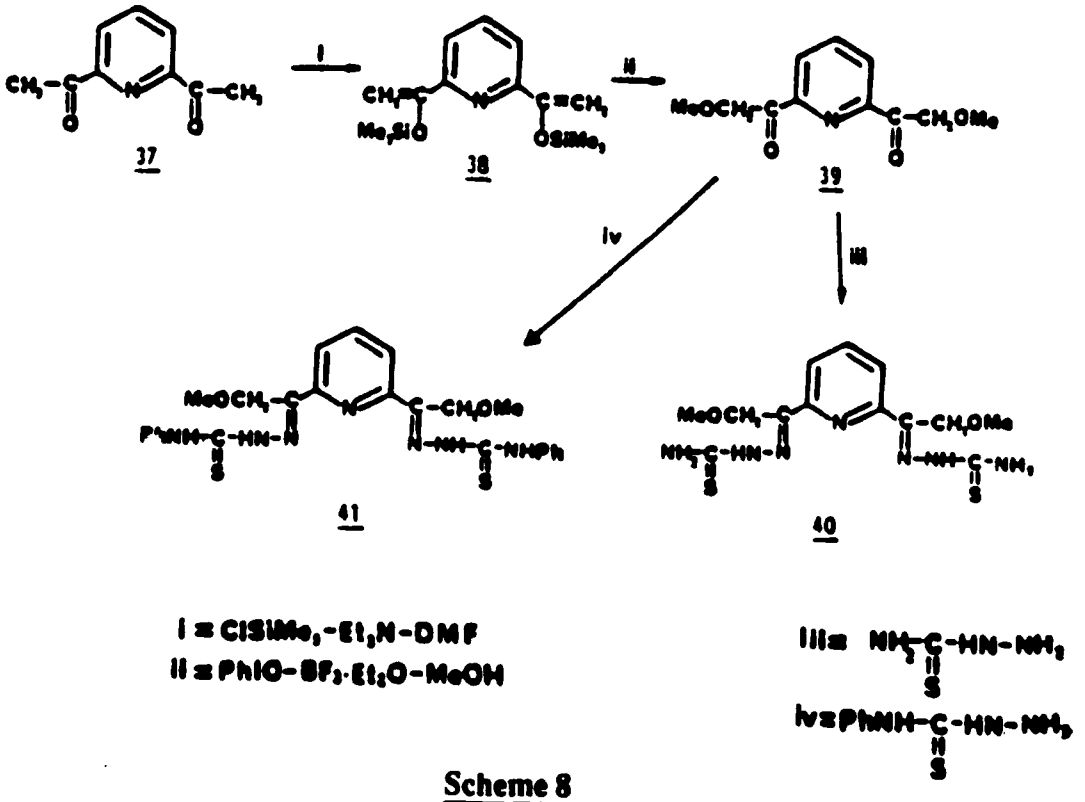
ii) **bis-Thiosemicarbazones of Pyridine**

In the pyridine series, first we synthesized the α-methoxy ketone (34) by treating trimethyl silyl enol ether[10] (33) with iodosobenzene in $BF_3 \cdot Et_2O$ and methanol.[11] α-Methoxy ketone (34) was converted to thiosemicarbazones (35 and 36) by treating it with either thiosemicarbazide or phenyl thiosemicarbazide (Scheme 7).



Scheme 7

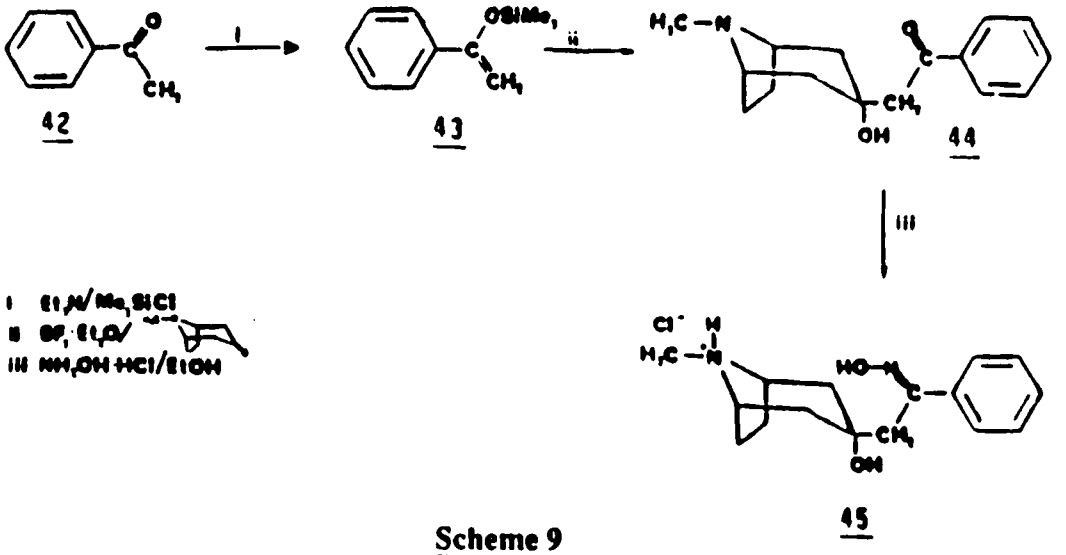
Secondly, 2,6-dimethoxymethylcarboxyl pyridine (39) was synthesized from trimethylsilyl enol ether 38 by the treatment of iodosobenzene in the presence of $BF_3 \cdot Et_2O$ and methanol. Dimethoxy ketone 39 was also converted to thiosemicarbazones (40 and 41) by treating it either with thiosemicarbazide or phenyl-thiosemicarbazide (Scheme 8).



Scheme 8

iii) Current and Ongoing Synthesis of Novel Reactivators

The final series of compounds being investigated has been started only recently. The parent ketone (44) was obtained by the condensation of acetophenone enol silyl ether (43) with tropan-3-one. This gives the aldol product (44) which was oximated (45) by refluxing with $NH_2OH.HCl$ in ethanol for one half hour (Scheme 9).



Scheme 9

The series is presently being expanded using substituted acetophenones and acetyl pyridines.

6. KINETIC STUDIES

Experimental: Assays

Acetylcholinesterase from the electric eel was purchased from Sigma Chemical Co., Dithiobisnitrobenzoic acid (DTNB), acetylthiocholine, and 2-PAM were purchased from Aldrich Chemical Co., Sephadex G-25 resin and TRIS buffer were also purchased from Sigma Chemical Co., Bio-Rad Dye was purchased from Sigma Chemical Co., and Boehringer-Mannheim Biochemicals.

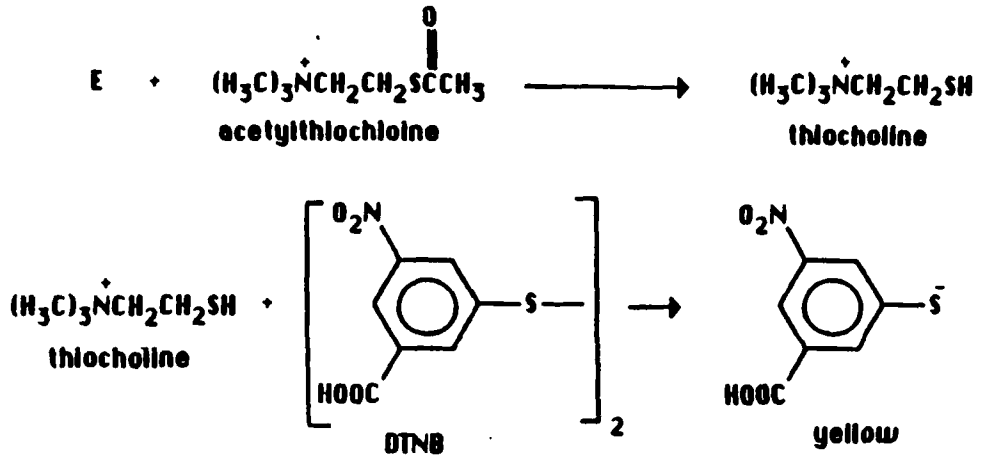
i) pKa Determination

A 25 mM aqueous solution of the oxime was titrated with 100 mM potassium hydroxide solution at 100 λ increments. The change in pH with each volume of base added was determined using the Henderson-Haselbach equation to calculate the pKa . The pKa is defined as the pH at which the species is 50% ionized.

ii) K_I Determination

Acetylcholinesterase stock solution was prepared by mixing 10λ of electric eel acetylcholinesterase from Sigma Chemical Co. having a specific activity of 1300 U/mg, and

containing 0.46 mg protein/ml in 1.99 ml of 100 mM TRIS buffer at pH 7.4. The rate of hydrolysis of the substrate, acetylthiocholine, was monitored at various concentrations (50, 100, and 300λ of 50 mM solution). The production of free thiocholine was determined by following change in O.D. at 412nm using DTNB as a coupler.



Each assay was then repeated using 50 and 100λ of 50 mM oxime solution, 10λ of the enzyme and the same series of acetylthiocholine concentrations in 100 mM TRIS buffer at a pH of 7.4. The volume in each cuvette never exceeded 3 ml total. In addition, blank experiments were performed to determing the interaction between substrate and the oxime at identical concentrations without enzyme.

The data was subjected to standard Michaelis-Menton kinetics for competitive inhibition. The Lineweaver-Burke (1/v vs. 1/S) plots were made and the slopes of these lines were replotted as slope vs. [I]. KI were determined from this plot and are listed in Tables 1 and 2.

iii) Inactivation Procedure

Acetylcholinesterase stock solution was prepared by a ten-fold dilution of commercial enzyme solution. Simultaneously, a DFP solution was prepared by adding 10λ of DFP to 900λ of absolute EtOH. This was diluted once more by adding 100λ to 400λ EtOH. The enzyme stock solution was passed through columns packed with Sephadex G-25 resin in 100 mM TRIS buffer at pH 7.4, to remove excess DFP. The inactivated enzyme was collected and pooled to ensure homogeneity.

iv) Reactivation Procedure

The inactivated enzyme, 200λ, was incubated with 100λ of 25 mM solutions of reactivator at room temperature and pH 7.4. After 2 hours, the solution was passed through a column packed with Sephadex G-25 resin to remove the reactivator from the solution. The enzyme was collected and assayed for activity using acetylthiocholine and DTNB. The formation of thiocholine was monitored as the change in O.D. at 412 nm.

Table 1. Binding Studies and Percentage Reactivation to 2-PAM for tropanone oxime methiodes.

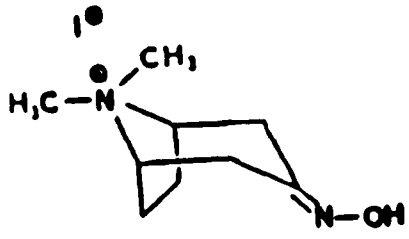
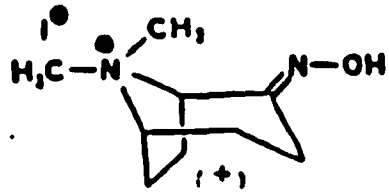
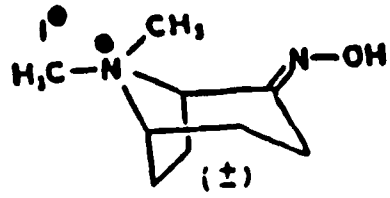
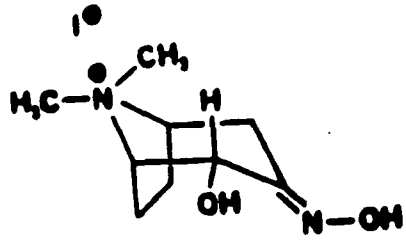
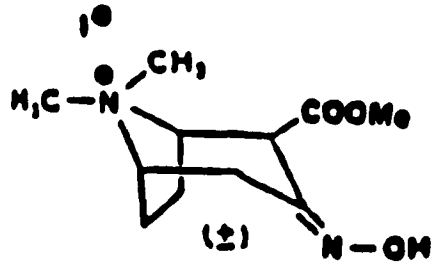
COMPOUND	NO.	pKa	Ki	REACTIVATION
	47	>11.0	1.78	-----
	49	>11.0	0.13	-----
	51	>11.0	0.18	-----
	55	>11.0	0.60	-----
	7e	10.8	0.385	-----

Table 1. (Continued)

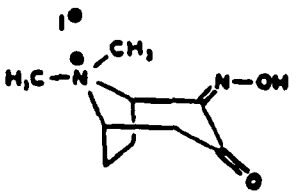
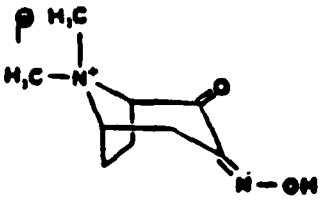
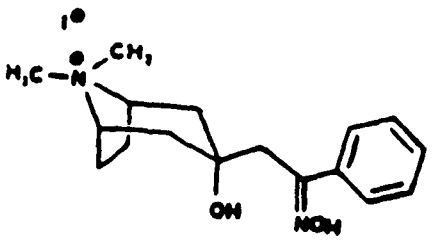
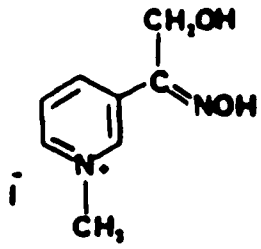
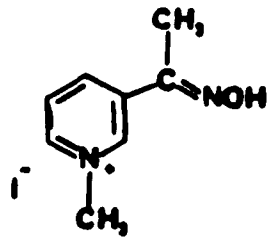
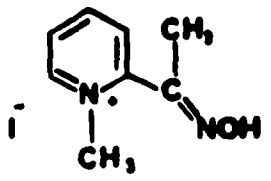
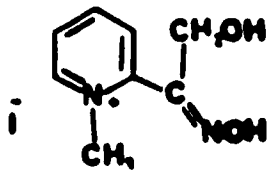
COMPOUND	NO.	pKa	Ki	REACTIVATION
	4	7.20	0.214	113%
	10	7.20	0.351	98%
	45	6.05	3.2	-----

Table 2: Binding Studies and Percentage Reactivation Relative to 2-PAM for Pyridine Oxime Methiodides

Compounds	pKa potentiometric spectra	K_I(mM)	%Reactivation
	7.5±0.2 7.8±0.1	0.07±0.01	100
	9.1±0.2 7.1±0.1	0.15±0.01	53
	9.8±0.2 10.2±0.2	0.04±0.01	22
	8.7±0.2 0.6	0.08±0.02	67

v) **Bradford Assay**

Each enzyme was treated with a 200λ aliquot of Bio-Rad dye to determine the exact amount of enzyme present. The dye contains Coomassie G-250 which gives a characteristic blue color that is proportional to the amount of protein present. The O.D. was measured at 595 nm in a quartz cuvette. The measurements were converted to μg/ml using a standard curve lyophilized acetylcholinesterase having a specific acitvity of 1000 U/mg, at specific concentrations.

In this manner, changes in the activity of the enzyme could be attributed directly to the ability of the oxime to reactivate the enzyme. Control experiments to determine the effect of column chromatography, incubation time, and reactivator on enzyme activity were performed concurrently. 2-PAM was studied in an identical fashion and all oximes were compared to it directly as the standard.

7. DISCUSSION OF KINETIC STUDIES

Initial pKa and binding studies on the three simple oximes; 3-tropinone oxime methiodide (47), (±) 2-tropinone oxime methiodide (49) and (±) 2-tropinone oxime methiodide (51, Table 1) established the crux of the problem. Although determination of the pKa's for these compounds proved difficult, the values were estimated to be greater than 11. The binding constants (K_i) however showed interesting variation. The larger the value of the inhibition constant, the less tightly it binds to the enzyme. The value found for the (±) isomer (51), was 0.18 mM, almost 1.4 times the value found for the (+) isomer (49), 0.13 mM. The ideal condition of course, would have been to find that the racemate had twice the value of the (+) isomer. This would mean that only one isomer would possess enzymatic activity. It is not surprising that the enzyme would show some preference in binding one enantiomer more tightly than the other. Whether this preference is extended to reactivators could not be determined from these oximes, because the pKa's were much too high to enable accurate assays to be performed. The problem to be solved initially was alteration of the oximes so as to stabilize the oximate anion and decrease the pKa as it is the oximate anion that reacts at phosphorus to regenerate the enzyme. By placing an electron withdrawing or electronegative group α to carbonyl, it was possible to accomplish this.

Preliminary studies (Table 1) of the two oximes (55) and (7e), showed that the effects of the α-hydroxy or α-carbomethoxy were not significant enough to decrease the pKa to the desired range of 7.0-7.6. The pKa of the α-hydroxy oxime (55) was found to be still greater than 11 and the α-carbomethoxy oxime (7e), was found to be 10.8. The binding constants were better than that found for 3-tropinone oxime methiodide (47) at 1.78 mM. For 55 the value was determined to be 0.60 mM and for 7e, the value 0.39 mM. Clearly the structure had to be further modified in order to increase the acidity of the oxime.

By placing a carbonyl function adjacent to the oxime this may be accomplished. Determination of pKa (Table 1) for the optically active and racemic 3-oximino 2-tropinone methiodided, (4) and

(10) respectively, gave identical values. The pKa was found to be 7.20 for both. The effect of an adjacent carbonyl proved to be enormous. The pKa was decreased by roughly five orders of magnitude. This means that these oximes are almost 100,000 times more acidic than the simple tropane oximes. The resonance contribution of the alpha carbonyl is many times more significant than any possible inductive effects of electronegative or electron withdrawing groups.

Preliminary studies showed the unsubstituted parent oxime hydrochloride (45), to have a pKa of 6.05. In addition competitive inhibition studies showed the binding constant to be 3.2 mM. Reactivation studies *in vitro* and *in vivo*, although dependent on such things as pKa and binding constants, are not totally predictable. The real question of whether or not these compounds may combine the parasympathetic effects of atropine with some ability to reactivate the enzyme may only be answered by *in vivo* studies. Similarly, the pKa's, binding studies and percentage reactivation for pyridine oxime methiodides were studied and are listed in Table 2.

8. SYNTHESIS AND CHARACTERIZATION OF COMPOUNDS

Materials: Nuclear magnetic resonance (NMR) spectra were recorded on a Varian A60 or EM360 spectrophotometer; chemical shifts are reported in parts per million (ppm δ) using tetramethylsilane (TMS) as standard. Unless otherwise mentioned, NMR spectra were recorded on solutions of the compounds in $CDCl_3$. Splitting patterns are designed as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Infrared (IR) spectra were obtained using a Unicam SP 1000 IR spectrophotometer. Melting points were determined on a Thomas Hoover capillary melting point apparatus and are uncorrected. Mass spectra (MS) were measured with a Hewlett Packard G/C/MS 5985 apparatus at 70 or 20 eV. Microanalyses were obtained from Micron Lab., Skokie, Illinois. All the new compounds gave satisfactory analyses (C, H, N).

Tetrahydrofuran (THF) was dried over $LiAlH_4$, distilled and stored over a 4A molecular sieve. Thin layer chromatography (TLC) was performed on pre-coated TLC sheets, silica gel 60 F-254 (layer thickness 0.2 mm, EM reagents). Column chromatography was done on silica gel (60-200 mesh), available from J. T. Baker Chemical Company.

Synthesis of (+) 3-Oximino tropan-2-one Methiodide (4)

(+) Ecoginine Hydrochloride (1a)

Cocaine hydrochloride (1, 14.0 g, 0.0415 mole) was refluxed in hydrochloric acid (500 ml, 0.75 N) for fifteen hours. Cooling caused crystallization of benzoic acid, which was removed by filtration and extraction with ether. The aqueous layer was evaporated to give ecoginine hydrochloride, 10.0 g. The crude salt was used in the following step without drying.

(+) Anhydroecoginine Amide (1b)

Crude (1a, 10.0 g,) was refluxed with $POCl_3$ (150 ml) for two and one half hours. The excess $POCl_3$ was removed at reduced pressure. The resulting viscous liquid was cooled to -78°C and NH_4OH was added slowly. The reaction was exothermic and frequent cooling was necessary. The

tan-brown solution was saturated with K_2CO_3 until a slurry formed. The slurry was extracted repeatedly with CH_2Cl_2 and the combined organic layers were dried and evaporated. The amide was obtained as a solid yielding 6.4 g. The crude solid was used as such in the following step.
m.p. 140°-142°C, [Lit.][1] m.p. 141°-144°C
% yield = 92 (based on cocaine)

(+) Tropan-2-one (2)

Amide (1b, 6.40 g, 0.038 mole) in methanol (50 ml) was cooled to -23°C and treated with NaOCl (43 ml, 0.75 M) and sodium hydroxide (2.07 g). The mixture was allowed to warm to room temperature and heated for fifteen minutes at 70°C. The mixture was cooled, diluted with H_2O and extracted with methylene chloride. The crude carbamate was refluxed with hydrochloric acid (200 ml, 6M) for one and one half hours. The solution was basified with NaOH (30 %) and the crude ketone was isolated from methylene chloride extracts. The crude ketone weighed 2.63 g.
m.p. 24°-27°C, [Lit.][1] m.p. 27°C
% yield = 45
IR (Nujol) cm^{-1}: 1720 (sharp C=O stretching)
^{1}H-NMR ($CDCl_3$) δ: 1.7-2.4 (m, 8H, 4xCH_2), 2.45 (s, 3H, N-CH_3), 3.6 (m, 2H, 2xCH)

(+) 3-Oximino Tropan-2-one (3)

Ketone (2, 2.63 g, 0.0189 mole) was added to a stirred solution of potassium t-butoxide (prepared from 1.75 g of potassium and dry t-BuOH) in dry t-BuOH under N_2. The solution changes color to dark red. t-BuONO (9.7 ml) was added and with stirring, a dark brown solution was formed. Stirring was continued over-night under N_2. t-BuOH was then removed under high vacuum and the solid residue was taken up in H_2O (80 ml). The dark brown solution was acidified with CO_2 to pH 6 and extracted with chloroform. Evaporation of the chloroform layer gave 0.59 g of crude α-oximino ketone 5.
% yield = 19
IR (Neat) cm^{-1}: 3350 (broad O-H stretching), 1720 (sharp, C=O stretching), 1680 (sharp, C=N stretching)
^{1}H-NMR ($CDCl_3$)δ: 2.4 (s, 3H, N-CH_3), 2.5-2.9 (m, 6H, 3xCH_2), 3.7 (m, 2H, 2xCH), 9.8 (s, 1H, OH)

(+) 3-Oximino Tropan-2-one Methiodide (4)

Oxime (3, 0.50 gm, 0.00298 mole) in $CHCl_3$ was allowed to stir at room temperaturewith an excess of methyl iodide in closed flask. After five hours, the solid that separated out was filtered to get 0.49 g (53%) of a pale yellow powder. The filtrate was allowed to sit overnight to collect 0.3 g of 6, total yield 0.79 g.
m.p. 208°-211°C (decomposition)
% yield = 85
IR (KBr) cm^{-1}: 3300 (broad O-H stretching), 1720 (sharp, C=O stretching), 1680 (sharp, C=N stretching)
^{1}H-NMR (D_2O)δ: 2.4-2.8 (m, 6H, 3xCH_2), 3.2 (s, 3H, CH_3), 3.3 (s, 3H, CH_3), 3.8 (m, 2H,

2xCH)

Analysis: $C_9H_{15}N_2O_2I$ requires (%) C=34.84, H=4.84, N=9.03, I=40.96 Found (%) C=35.15, H=4.78, N=9.36, I=40.45

Preparation of Racemic 3-Oximino Tropan-2-one Methiodide

(±) 2-Carbomethoxy tropan-3-one (7)[2]

i) **β-Ketoglutaric anhydride[2]**

β-Ketoglutaric acid (160 g, 1.09 mole) was stirred at -10°C in a mixture of acetic anhydride (172 ml) and acetic acid (240 ml). After three hours the crude anhydride was filtered and washed with benzene to yield 128 g of β-ketoglutaric anhydride.

% yield = 88

ii) **β-Ketoglutarate monomethyl Ester[2]**

The above anhydride (128 g, 1.0 mole) was dissolved in cold methanol (500 ml) giving a solution of monomethyl ester in MeOH.

iii) **Succindialdehyde[2]**

2,5 dimethoxytetrahydrofuran (105 ml, 107.1 g, 0.8 mole) was stirred in H_2SO_4 (500 ml, 0.1 M) at room temperature under N_2. After three hours, the solution was neutralized with of $BaCO_3$ (32 g). The resulting $BaSO_4$ was filtered to get a solution of the dialdehyde. Succindialdehyde which was used immediately.

iv) **(±) 2-Carbomethoxy Tropan-3-one (7)[2]**

Methylamine hydrochloride (80 g, 1.194 mole) and NaOH was (32 g, 0.80 mole) was dissolved in H_2O (5 l). To this mixture was added the methanolic solution of β-ketoglutarate monomethyl ester. The aqueous solution of succindialdehyde (500 ml of ~ 1.25 mole) was then added dropwise. The slow evolution of CO_2 was observed. The solution was allowed to stir at room temperature for twenty four hours. The mixture ceased to evolve CO_2 and acquired a deep yellow color. This was acidified to pH 3 with dilute HCl and washed with $CHCl_3$ to remove resinous by-products. Then the solution was made alkaline with 4N NaOH (80 ml, 4 N) and $NaHCO_3$ to pH 8.

The mixture was extracted with $CHCl_3$, combined organic layers were dried over anhydrous $MgSO_4$ and evaporated, to give a brown oil that was crystallized with aqueous acetone to 27.64 g of 7 in the first crop. Second crystallization gave 39.25 g of pale yellow solid, for a total of 66.89 g.

m.p. = 99° - 100°C [Lit][2] = 99° - 100°C

% yield = 34

(±) Allopseudoecoginine methyl ester (7a)[3]

2-Carbomethoxy tropan-3-one, (25 g, 0.127 mole), was dissolved in MeOH (750 ml) at -23°C, $NaBH_4$ (25 g, 0.657 mole) was added in three portions.Vigorous H_2 evolution was observed and the solution was kept for three and one half hours while slowly warming to room

temperature. The reaction was quenched with conc. HCl, acidified to pH 4 and washed with Et_2O. The solution was re-basified with aqueous ammonia to pH 8 and extracted with $CHCl_3$. The combined extracted were dried and evaporated to give 15.62 g of crude alcohol 7a as a yellow-brown oil.

% yield = 62

(±) Ecoginine hydrochloride (7b)[3]

Allopseudoecoginine methyl ester, 7a, (15.0 g, 0.075 mole) was refluxed in 350 ml of dilute HCl (400 ml, 0.75 N) over-night. The aqueous solution was evaporated to give a dark brown solid weighing 17.1 g (damp) of 7b. The crude acid salt was used without drying.

(±) Anhydroecoginine amide (7c)[3]

Crude ecoginine from the previous step was refluxed in 200 ml of $POCl_3$ for two hours and excess reagent was removed under reduced pressure. The dark brown viscous oil was cooled to -77°C and quenched with conc. NH_4OH. The exothermic reaction was cooled in the dry ice-acetone bath periodically to control the rate of reaction. The brown-yellow solution was then carefully saturated with K_2CO_3 and exhaustively extracted with $CHCl_3$. Evaporation of $CHCl_3$ gave 6.0 g of 7c. This was used as such in the next step.

% yield = 36

(±) Tropan-2-one (8)

To a solution of anhydroecoginine amide (7c, 6.0 g, 0.036 mole) in MeOH (125 ml) at -23°C, a solution of NaOCl (37.5 ml, 0.75 N) and NaOH (1.75 g) was added with stirring. The mixture was allowed to warm to room temperature and heated for fifteen minutes at 70°C. After diluting with H_2O, the solution was extracted with $CHCl_3$. Evaporation of the $CHCl_3$ layer gave 5.8 g of oily carbamate. The carbamate was refluxed in HCl (200 ml, 6N) for one and one half hours. The reaction mixture was cooled, basified with 30% NaOH and extracted with $CHCl_3$ to give 1.93 g of crude ketone 8. The product was used without further purification.

% yield = 38

(±) 3-oximino tropan-2-one (9)

Ketone 8 (1.4 g, 0.0101 mole) was added with stirring to a solution of t-BuOK (prepared from 1 g of potassium and dry t-BuOH) in dry t-BuOH. The solution changed color after the addition of 6.5 ml t-BuONO and stirring was continued overnight. After removal of the solvent, the solid residue was taken up in a minimum amount of water and acidified with CO_2. Extraction with $CHCl_3$ gave 0.13 g of crude oxime 9.

% yield = 8

IR (Nujol) cm^{-1}: 3350 (broad O-H stretching), 1720 (sharp C=O stretching), 1640 (sharp, C=N stretching)

^{1}H-NMR ($CDCl_3$)δ: 2.2-2.9 (m, 6H, 3xCH_2), 2.5 (s, 3H, CH_3), 3.8 (m, 2H, 2xCH), 9.8 (s, 1H, OH)

(±) 3-Oximino Tropan-2-one Methiodide (10)

Oxime (9, 0.10 g, 0.00059 mole) in $CHCl_3$ was allowed to sit at room temperature with excess methyl iodide. Filtration gave 0.148 g of solid.

m.p. 194°-196°C (decomposition).

% yield = 80

IR (KBr) cm^{-1}: 3300 (broad O-H stretching), 1710 (sharp C=O stretching), 1650 (sharp C=N stretching)

^{1}H-NMR (D_2O)δ: 1.8-2.8 (m, 6H, 3xCH_2), 2.9 (s, 3H, N-CH_3), 3.0 (s, 3H, N-CH_3), 3.9 (m, 2H, 2xCH)

Analysis: $C_9H_{15}N_2O_2I$ requires (%) C=38.84, H=4.84 N=9.03, I=40.96. Found (%) C=38.05, H=4.99 N=8.83, I=41.09

Preparation of 2-Carbomethoxyl Tropan-3-one Oxime Methiodide (7e)

2-Carbomethoxytropan-3-one Methiodide (7d)

Racemic 2-carbomethoxytropan-3-one (7, 2.0g, 0.01 mole) was dissolved in 150 ml THF and stirred with excess CH_3I. The solution became cloudy with precipitate. Filtration gave 3.05 g of the methiodide,

m.p. 183°-186° (decomposition)

% yield = 90

2-Carbomethoxytropan-3-one Oxime Methiodide (7e)

The methiodide (7d 3.0 g, 0.0152 mole) dissolved in methanol was stirred with one equivalent of NH_2OH (0.62 g NH_2OH.HCl and 0.5 g KOH in methanol). Removal of methanol after twenty four hours gave a solid 3.22 g.

m.p. 155°-157°C (decomposition)

% yield = 93

IR (Nujol) cm^{-1}: 1740 (sharp C=O stretching), 1660 (sharp C=N stretching)

^{1}H-NMR (D_2O)δ: 2.0-2.8 (m, 6H, 3xCH_2), 3.1 (s, 3H, CH_3), 3.2 (s, 3H, CH_3), 3.75 (s, 3H, $COOCH_3$), 4.1 (m, 3H, 3xCH)

Analysis: $C_{11}H_{19}N_2O_3I$ requires (%) C=37.29, H=5.36, N=7.91, I=35.88. Found (%) C=36.98, H=5.17, N=8.17, I=35.20

Preparation of (±) 2-Oximino Tropan-3-one Methiodide (17)

(±) 2-Oximino Tropan-3-one Hydrochloride (15)

Tropan-3-one (13, 6.95 g, 0.05 mole) was dissolved in MeOH (100 ml) and conc. HCl (5 ml). After stirring for fifteen minutes, t-BuONO (20.5 ml) was added cautiously to the solution.

Vigorous reaction took place with a fading in color of the solution. Stirring was continued at room temperature. The solution was filtered after five days to yield 6.75 g of hydrochloride 15.

m.p. 230°-232°C

% yield = 66

IR (Nujol) cm^{-1}: 3400-3200 (broad O-H & N-H stretchings), 1713 (sharp C=O stretching), 1660 (sharp, C=N stretching)

^{1}H-NMR (D_2O)δ: 2.2-2.9 (m, 6H, 3xCH_2), 3.0 (s, 3H, N-CH_3), 4.0 (m, 2H, 2xCH)

Analysis: $C_8H_{13}N_2O_2Cl$ requires (%) C=46.94, H=6.36, N=13.69, Cl=17.36 Found (%) C=46.41, H=6.08, N=14.01, Cl=16.98

(±) 2-Oximino Tropan-3-one Methiodide (17)

The above hydrochloride 15, (2.0 g, 0.0098 mole) was dissolved in 100 ml of EtOH and 1 equivalent of conc. NH_4OH. After dissolution of the solid, EtOH was evaporated. Removal of the solvent gave a brown solid which contained NH_4Cl. The solid was triturated with excess CH_3I. After fifteen minutes, the solution became cloudy. The solution was allowed to sit overnight. Solid was collected by filtration, 1.05 g, as a pale yellow powder.

m.p. 205-210°C (decomposition)

% yield = 34

IR(KBr)cm^{-1}: 3350-3150 (broad N-H, O-H stretchings), 1710 (sharp C=O stretching), 1660 (sharp, C=N stretching)

^{1}H-NMR (DMSO.d_6)δ: 2.2-2.9 (m, 6H, 3xCH_2), 3.0 (s, 3H, CH_3), 3.1 (s, 3H, CH_3), 4.1 (m, 2H, 2xCH)

Analysis: $C_9H_{15}N_2O_2I$ requires (%) C = 34.84, H = 4.84, N = 9.03, I = 40.96 Found (%) C = 34.61, H = 5.01, N = 9.13, I = 41.24

2,4-Dimethoxy Tropan-3-one (18)

A solution of tropan-3-one (2, 1.39 g, 0.01 mole) in methanol was added dropwise with stirring to a cold solution (0°C) of potassium hydroxide (1.68 g, 0.03 mole) in methanol (30 ml). After the addition, the solution was stirred for fifteen minutes and then iodobenzene diacetate (3.22 g, 0.01 mole) was added in small portions over a period of thirty minutes. The reaction mixture was stirred at 0°C for two hours and at room temperature overnight. The reaction mixture was extracted with ether, washed with saturated NH_4Cl solution and dried over anhydrous $MgSO_4$. Evaporation of the ether layer gave a residue which was chromatographed to get the title compound 18.

m.p. 38°-40°C

% yield = 20

IR (KBr) cm^{-1}: 1730 (sharp C=O stretching)

^{1}H-NMR ($CDCl_3$)δ: 1.8-2.4 (m, 4H, 2xCH_2), 2.5 (s, 3H, N-CH_3), 3.3 (s, 6H, 2xOCH_3), 5.9 m, 4H, 4xCH)

2,4-Dimethoxy-3-oximinotropane methiodide (20)

A mixture of 18 (1.99 g, 0.01 mole) and hydroxylamine (0.33 g, 0.01 mole) in methanol (20 ml) was stirred at room temperature overnight. The solid 19 was taken in CH_2Cl_2 (500 ml) and treated with methyl iodide (3 ml). The reaction mixture was stirred for twenty-four hours. The solid which separated out was collected by filtration to yield 1.284 g of 20.

m.p. 257°-260°C

% yield = 60

IR(KBr)cm^{-1}: 3240 (broad O-H stretching), 1640 (sharp C=N stretching)

^{1}H-NMR (DMSO.d_6)δ: 1.8-2.4 (m, 4H, 2xCH_2), 3.0 (s, 3H, N-CH_3), 3.1 (s, 3H, CH_3), 3.3 (s, 6H, 2xOCH_3), 4.2 (m, 4H, 4xCH)

Analysis: $C_{11}H_{21}N_2O_3I$ requires (%) C = 37.07, H = 5.89, N = 7.86, I = 35.67, Found (%) C = 37.01, H = 5.73, N = 7.77, I = 35.82

Preparation of 1-(1',1'-Dimethyl 4'-phenylpiperidinyl)-4-piperiodone) oxime iodide (26)

1-(1'Methyl 4'-cyanopiperidinyl) piperidone ethylene ketal (22)

A solution of sodium bisulfite (86.0 g, 0.827 mole) in water (200 ml) was added to 1-methyl 4-piperidone (31, 90.5 g, 0.799 mole). The solid was separated out immediately. After one hour, a mixture of sodium cyanide (42 g, 0.7 mole) and 4-piperidone ethylene ketal (114.2 g, 0.799 mole) in water (100 ml) was added. The solid bisulfate product dissolved and the solution was stirred at room temperature for twenty-four hours. The crude white solid was collected by filtration, yielding 177.27 g.

m.p. 128°-130°C

% yield = 84

1-(1'-Methyl 4'-phenyl piperidinyl) piperidone ethylene ketal (23)

Carbonitrile (22), 170 g, 0.642 mole) was dissolved in dry ether (300 ml) and was added dropwise with stirring to a solution containing approximately 1.5 equivalents of phenylmagnesiumbromide (174.3 g, 0.963 mole). After twenty-four hours a white solid was separated out. Saturated ammonium chloride (500 ml) was added to the reaction mixture and stirred for four hours. The ethereal layer was separated, dried with anhydrous $MgSO_4$ and evaporated to give crude 23, yield 42.2 g (20%). The ketal was recrystallized from ethanol, yield 36.6 g.

m.p. 144°-146°C

% yield = 17

1-(1'-Methyl 4'-phenyl piperidinyl)piperidone (24)

Ketal 23 (35.0 g, 0.111 mole) was dissolved in HCl (200 ml) and stirred at room temperature for twenty-four hours. The acid solution was neutralized with conc. NH_4OH at 0°C. At pH 7 the solution was saturated with NH_4Cl and extracted with ether. The combined ethereal layers were dried, filtered and evaporated to give 24, yield 8.0 g.

% yield = 25

1-(1'-Methyl 4'-phenylpiperidinyl)piperidone oxime (25)

A mixture of ketone 24 (4.0 g, 0.021 mole) and hydroxyl amine (0.957 g, 0.029 mole) in methanol (20 ml) was stirred at room temperature for two hours by which time the ketone had dissolved. Stirring was continued for an additional two hours, by which time a white solid was precipitated out of the methanol. The reaction mixture was cooled and filtered to get 3.1 g of 21.

m.p. 245°-247°C

% yield = 47

IR(Nujol)cm^{-1}: 1710 (sharp C=O stretching)

^{1}H-NMR (DMSO-d_6)δ: 1.7-1.9 (m, 4H, 2xCH_2), 2.1-2.6 (m, 12H, 6xCH_2), 2.5 (s, 3H, CH_3), 7.3 (s, 5H, aromatic protons)

1-(1';1'-Dimethyl 4'-phenylpiperidinyl)-4-piperidone oxime iodide (26)

Oxime 25 (1.6 g, 0.0076 mole) was dissolved in CH_2Cl_2 (160 ml) and methyliodide (3 ml) was added. The solution was left at room temperature for twenty-four hours. The solid which separated out was collected by filtration, 2.1 g.

m.p. 257°-258°C

% yield = 88

IR (KBr) cm^{-1}: (broad O-H stretching), 1665 (sharp C=N stretching)

^{1}H-NMR (DMSO-d_6)δ: 1.7-1.9 (m, 4H, 2xCH_2), 2.3 (m, 8H, 4xCH_2), 3.0 (m, 4H, 2xCH_2), 3.05 (s, 3H, N-CH_3), 3.1 (s, 3H, CH_3), 7.3 (s, 5H, aromatic protons)

Preparation of 1-methyl 3-oximino- 5,5- diphenyl 1-azacycloheptan-4-one methiodide (31)

4-Hydroxy-1-methylisonipectonitrile

1-Methyl 4-piperidone, 10 g, was added to a cold saturation solution of 12 g KCN in H_2O. The mixture became semi-solid within one minute and dilute HCl was added with cooling to acidify the solution. The mixture was the neutralized with K_2CO_3 and 5 g excess was added to salt out the product. The aqueous solution was extracted with ether, and evaporated to give 10.7 g cyanohydrin.

m.p. 135°-42°C, [Lit.][9]; m.p. 135°-138°C

% yield = 87

Ethyl 4-hydroxy-1-methylisonipectoate

To a benzene solution of 7 g of the cyanohydrin, was added 16 ml conc. HCl. The contents were refluxed for five hours. The solvent was removed and the solid residue was dried by distillation of benzene from it. The solid was taken up in 80 ml EtOH and 8 ml H_2SO_4 and heated at reflux for 5 hrs. The sulfuric acid was neutralized by addition of Na_2CO_3 to the cooled mixture. The semi-solid mass was extracted with ether. After drying over Na_2SO_4 the ether was evaporated to give an oil weighing 6.5 g.

% yield = 70

4-Hydroxy-1-methyl-4-piperidyl diphenyl carbinol (28)

A solution of 6.2 g of the above ester in dry ether was added dropwise to a solution of phenyl

lithium (~8 x excess). After addition was complete, the reaction mixture was heated at reflux for four hours and allowed to stand twelve hours. The reaction mixture was poured into water giving 8.89 g of the product as a precipitated solid.

m.p. 154°-159°C, [Lit.][9] m.p. 160°C

% yield = 94

IR (Nujol) cm^{-1}: 3300 (broad O-H stretching)

^{1}H-NMR (DMSO-d_6)δ: 1.7-1.9 (m, 4H, 2xCH_2), 2.4 (m, 4H, 2xCH_2), 2.5 (s, 3H, CH_3), 7.3-7.8 (m, 1 OH, aromatic protons)

1-Methyl 5,5-diphenyl 1-azacycloheptan-4-one (29)

The diol (28, 4.0 g, 0.019 mole) was added in small portions to 16 ml conc. H_2SO_4 at 0°C with stirring. After three hours the black viscous solution was added to 40 ml H_2O and made basic with K_2CO_3. The mixture lost its color and became thick with precipitate. The solution was filtered and washed thoroughly with more H_2O. The solid was triturated with Et_2O. The ethereal solution was dried over $MgSO_4$ and evaporated to give 2.45 g of ketone

m.p.85°-88°C, [Lit.][9] m.p. 87°-88°C

% yield = 66

IR (KBr) cm^{-1}: 1710 (sharp C=O stretching)

^{1}H-NMR (DMSO-d_6)δ: 1.8 (t, 2H, CH_2), 2.1 (t, 2H, CH_2), 2.4 (m, 4H, 2xCH^2), 2.5 (s, 3H, CH_3), 7.3-7.8 (m, 1OH, aromatic protons)

1-Methyl-3-Oximino 5,5-diphenyl 1-azacycloheptan-4-one (30)

Ketone (29, 2.2 g, 0.0083 mmol) was added to a stirring solution of 0.53 g potassium in dry t-BuOH. After fifteen minutes 3.5 ml of t-BuONO was added and the mixture was stirred overnight. The t-BuOH was removed under reduced pressure and the solid residue was taken up in H_2O. The aqueous solution was acidified with CO_2 until precipitation was complete. After filtration, solid was dissolved in $CHCl_3$, and was crystallized. The crystalline puff weighed 1.63g.

m.p. 74-74°C

% yield = 67

IR (Nujol) cm^{-1}: 3300 (broad O-H stretching), 1710 (shape C=0 stretching), 1655 (shape C=N stretching)

^{1}H-NMR ($CDCl_3$)δ: 2.2-2.8 (4H, 2xCH_2), 2.3 (s, 3H, N-CH_3), 3.6 (s, 2H, CH_2), 7.3-7.8 (m, 1OH, aromatic protons)

1-Methyl 3-oximino 5,5-diphenyl 1-azacycloheptan-4-one Methiodide (31)

The α-keto oxime 30 (1.6 g, 0.0052 mmol) was dissolved in CH_2Cl_2 and allowed to sit at room temperature in a stoppered flask in the presence of excess CH_3I. After one week, filtration gave 1.2 g of solid. The filtrate was allowed to sit an additional five days. Filtration again gave 0.32 g for a total of 1.52 g of the methiodide.

m.p. 214°-215°C (decomposition)

% yield = 65

IR (Nujol)cm^{-1}: 3300 (broad O-H stretching), 1710 (shape C=O stretching)

^1H NMR (DMSO-d_6)δ: 2.2-2.8 (m, 6H, 3xCH_2), 2.9 (s, 3H, CH_3), 3.0 (s, 3H, CH_3), 7.2-7.8 (m, 10H, aromatic protons), 9.8 (br, 1H, NOH)

Analysis: $C_{20}H_{23}N_2O_2I$ requires (%) C = 53.03, H = 5.11, N = 6.22, I = 28.22. Found (%) C = 52.69, M = 5.10, N = 5.97, I = 27.88

2-(Methoxymethylcarbonyl)pyridine (34)

Boron trifluoride etherate (17.00 g; 0.12 mol) was dissolved in dry dichloromethane (500 ml) and iodosobenzene (9.68 g, 0.044 mol) was added. The mixture was cooled to -70°C and then silyl enol ether 33 (7.72 g, 0.040 mol) was added, followed by methanol (10 ml). The reaction mixture was stirred at -70°C for one hour. The temperature was then slowly raised to room temperature. Stirring was continued for another thirty minutes. Water (50 ml) was added and mixture was basified with a saturated solution of sodium bicarbonate and then transferred to a separatory funnel. The aqueous layer was extracted with dichloromethane (4 x 50 ml). The organic phases were combined, dried over magnesium sulfate and concentrated *in vacuo* to yield the crude product which did not show any starting material (by TLC and NMR). Distillation of crude product afforded pure 34, 4.24 g. (Some portion of the product decomposes during distillation, higher temperature for distillation are not recommended).

b.p. 82-83°C/0.05 mm

% yield = 70

NMR($CDCl_3$)δ: 3.53 (s, 3H, OCH_3), 5.02 (s, 3H, CO-CH_2), 7.30-8.05 (m, 3H, pyridine protons), 8.62-8.80 (m, 1H, pyridine proton)

Analysis: $C_8H_9NO_2$ requires (%) C, 63.58; H, 5.96; N, 9.27 Found: C, 63.29; H, 6.10; N, 9.11

MS (m/z): 151 (M^+, 10), 136 (100)

2-(Methoxymethylcarbonyl)pyridine Thiosemicarbazone (35)

2-(Methoxymethylcarbonyl)pyridine (1.51 g, 0.01 mole) was dissloved in 100 ml of methanol. To this was added (0.61 g, 0.01 mol) of thiosemicarbazide. The contents were allowed to reflux for two and one half hours and the reaction mixture was allowed to cool at room temperature. The product obtained was filtered and crystallized with methanol, yielding 1.95 g.

m.p. 138°C

% yield = 87

IR (KBr) cm^{-1}: 3395, 3290 (sharp N-H stretching)

^1H NMR ($CDCl_3$)δ: 3.38 (s, 3H, OCH_3), 4.47 (s-$COCH_2$), 7.33-8.0 and 8.70-8.91 (m, 4H, aromatic protons)

Analysis: $C_{19}H_{12}N_4O_5$ requires (%) C = 48.21; H = 5.36; N = 25.00; S = 14.2 g; Found (%) C = 47.82; H = 5.3 g; N = 25.06; S = 14.37

MS (m/z): 224 (M^+-30)

2-(Methoxymethylcarbonyl)pyridine-4'-phenylthiosemicarbazone (36)

2-(Methoxymethylcrbonyl)pyridine (1.51 g, 0.01 mol) was dissolved in 100 ml of methanol.

To this 1.67 g (0.01 mol) of phenyl thiosemicarbazide was added. The contents were refluxed for four hours. The reaction mixture was allowed to cool to room temperature. The product was filtered, washed with methanol and crystallized from the methanol, yielding 2.4 g.

m.p. 113-115°C

% yield = 80

IR(KBr)cm^{-1}: 3240, 3190 (sharp N-H stretchings)

NMR($CDCl_3$)δ: 3.50 (s, OCH_3), 5.08 (s, $-COCH_2$), 7.20-8.12 and 9.61-8.70 (m, 4H, aromatic protons)

Analysis: $C_{15}H_{16}N_4OS$ requires (%) C = 60.0; H = 5.33; N = 18.66; S = 10.66; Found (%) C = 59.59; H = 5.50; N = 18.5 g; S = 10.86

MS(m/z): 300 (M^+, 30)

2,6-Bis-(Methoxymethylcarbonyl)pyridine (39)

In this case, silyl enol ether (38) (6.16 g, 0.02 mole) was treated with iodosobenzene (8.8 g, 0.04 mole), boron trifluoride etherate (11.36 g, 0.08 mole) and 10 ml of methanol in 500 ml of dry dichloromethane. To the crude mixture (obtained in 34) was added hexane (50 ml). The resulting mixture was allowed to stand for a few minutes, filtered and cooled slowly to about 10°C. After thirty minutes, colorless crystalline product (2.67 g (60%), mp 100-101°C) was collected by filtration and drying. Recrystallization from hexane gave analytical sample. Filtrates gave further amounts of the product. The total amount of the product was 3.16 g.

m.p. 101-102°C

% yield = 71

^1H NMR($CDCl_3$)δ: 3.55 (s, 6H, two-OCH_3), 5.05 [s, 4H, $(C(=O)-CH_2)_2$], 8.05-8.40 (m, 3H, pyridine protons)

Analysis: $C_{11}H_{13}NO_4$ requires (%) C = 59.19; H = 5.83; N = 6.28; Found: (%) C = 58.74; H = 5.80; N = 6.29

MS(m/z): 223 (M+, 10), 208.4(100), 192(8), 176(18), 134(27), 105(20)

2,6-Bis(Methoxymethylcarbonyl)pyridine bisthiosemicarbazone (40)

To a methanolic solution of 2,6-bis-(methoxymethylcarbonyl)pyridine (2.08 g, 0.01 mole) was added 1.82 g (0.02 mole) of thiosemicarbazide. The contents were refluxed for four hours. The reaction mixture, on cooling, afforded the 2,6-bis-(methoxymethylcarbonyl)pyridine-bis-thiosemicarbazone, yielding 2.5 g.

m.p. 211°-212°C

% yield = 71

IR(KBr)cm^{-1}: 3160, 3250, 3395

Analysis: Calculated for $C_{13}H_{19}N_7O_2S_2$: C = 42.28; H = 5.15; N = 26.56; S = 17.34; Found: C = 41.12; H = 4.87; N = 26.64; S = 17.52

MS (m/z): 369 (M^+, 20)

2,6-bis(Methoxymethylcarbonyl)pyridine bis-4-phenylthiosemicarbazone (41)

2.8 g (0.01 mole) of 2,6-bis(methoxymethylcarbonyl)pyridine was dissolved in methanol. To this solution was added 3.74 g (0.02 mole) of phenylthiosemicarbazide. The contents were refluxed for four hours, then left at room temperature for two hours. The solid was filtered and crystallized from methanol, yielding 4.5 g.

mp. 190-193°C

% yield = 89

Analysis: $C_{25}H_{27}N_7O_2S_2$ requires (%): C = 57.57; H = 5.18; N = 18.81; S = 12.31; Found (%): C = 56.93; H = 5.11; N = 18.49; S = 12.14

IR(KBr)cm^{-1}: 3300, 3285

MS (m/z): 521 (M^+, 100)

Preparation of 3-Acetophenyl Tropineoxime Hydrochloride (45)

3-Acetophenyl Tropine (44)

To a solution of trimethylsilyl enol ether (43) derived from acetophenone (42) (6.6 g, 0.036 mole) in dry CH_2Cl_2 (from P_2O_5), tropinone (5.0 g, 0.03597 mole) was added in one portion followed by $BF_3.ET_2O$ (2.2 equiv.) *via* syringe. The reaction mixture was stirred vigorously for three and one half hours during which time a viscous gum settled out. The reaction mixture was cautiously quenched with of saturated $NaHCO_3$ (75 ml). A solid appeared in the two-phase system later found to be a borate complex of the condensation product. Vigorous stirring of the mixture broke up much of this complex. The layers were separated. The CH_2Cl_2 layer was dried and evaporated giving an oil that contains unreacted tropinone and product. Swirling of the oil with 1:1 ether and hexane allowed the crystallization of the aldol 44 as transparent, buff-colored crystals, yielding 1.42 g.

m.p. 95°-98°C

% yield = 15

IR (Nujol)cm^{-1}: 3480 (broad O-H stretching)

NMR ($CDCl_3$)δ: 1.18-2.5 (m, 8H, 4xCH_2), 2.5 (s, 3H, NCH_3), 3.1 (s, 2H, CH_2), 3.1-3.3 (m, 2H, 2xCH), 4.05 (s, 1H, OH), 7.3-8.2 (m, 5H, aromatic protons)

3-Acetophenyl Tropine Oxime Hydrochloride (45)

Ketone 44 (0.6 g, 0.00231 mole) was dissolved in absolute ethanol and refluxed with stirring of $NH_2OH.HCl$ (0.159 g; 0.00231 mole) for one hour. After cooling the reaction mixture, ethanol was evaporated which left a crude yellow white solid. Stirring with cold ethanol and filtration gave 0.54 g of white powder.

mp 246°-248°C (decomposition)

% yield = 85

IR (Nujol) cm^{-1}: 3400 (broad O-H stretching), 1579 (sharp C=N stretching)

^1H NMR(D_2O)δ: 2.1-2.5 (m, H, 4xCH_2) 2.6 (s, 2H, CH_2), 3.0 (s, 3H, CH_3), 3.9 (m, 2H, 2xCH), 7.75 (m, 5H, aromatic protons)

Synthesis of 3-Tropinone Oxime Methiodide (47)

3-Tropinone Oxime (46)

The ketone 3-tropinone (3.0 g, 0.0215 moles) was dissolved in 60 ml of absolute methanol and stirred with one equivalent of hydroxylamine hydrochloride, 1.45 g, at room temperature overnight. Vacuum-assisted filtration gave 3.81 g of a white solid, a 91% yield. The salt was dissolved 30 ml of H_2O and treated with Na_2CO_3. Extraction with chloroform, drying and evaporation of solvent gave 2.6 g of the free oxime.

mp. 112-113°C (Lit.[12] mp. 110-111°C)

% yield = 83

MS (m/z): M/e 154(M^+), 137, 109, 96, 82

3-Tropinone Oxime Methiodide (47)

A solution of the oxime (46), 2.0 g, 0.013 moles, in 75 ml chloroform was treated with an excess of methyl iodide. After three hours filtration gave 3.42 g of product.

mp. 235-262°C (decomposition)

% yield = 89

NMR(D_2O)δ: 3.26 3.13 (6H, N-Me_2), 3.95 (2H, CH_2)

Analysis: (%) Calc., C: 36.73, H: 5.10, N: 9.52, I: 43.20. Found (%): C: 36.44, H: 5.31, N: 9.28, I: 43.62

Synthesis of (+) 2-Tropinone Oxime Methiodide (49)

(+) 2-Tropinone Oxime Hydrochloride (48)

The ketone (+) 2-tropinone (2) (1.0 g, 0.007 moles) was added to a stirring soution of 0.49 g of hydroxylamine hydrochloride in 25 ml of absolute ethanol. The solution immediately filled with a white solid. Stirring was continued for two hours. Filtration gave 0.94 g of a white solid.

mp. 220°C

(+) 2-Tropinone Oxime Methiodide (49)

Oxime hydrochloride 52 (0.80 g, 0.0042 moles) was dissolved in a minimum amount of water and basified with sodium bicarbonate, and extracted with chloroform. The organic layers were dried with magnesium sulfate and evaporated. The oxime was isolated as a white solid weighing 0.62 g, mp. 143-145°C. The oxime (0.60 g, 0.0039 moles) was dissolved in 20 ml dry chloroform and stirred at room temperature with an excess of methyl iodide. Within minutes, the solution filled with a white solid. Filtration gave 0.88 g of the methiodide.

mp. 220-222°C (decompostotion)

NMR(DMSO-d_6)δ: 11.4 (1-H), 3.4 (N-Me_2)

Analysis: Calc., C: 36.73, H: 5.10, N: 9.52, I: 43.20. Found (%): C: 36.36, H: 5.31, N: 9.24, I: 43.56

Synthesis of (±) 2-Tropinone Oxime Methiodide (51)

(±) 2-Tropinone Oxime (50)

Racemic 2-tropinone (8, 0.20 g, 0.0014 moles) was dissolved in 15 ml absolute methanol. To

this solution was added a solution of hydroxylamine made from 0.10 g hydroxylamine hydrochloride and 0.08 g KOH in 10 ml MeOH. The resultant KCl was filtered away. After 2 hours at room temperature, removal of the solvent gave 0.120 g of the oxime as a pale yellow solid.

mp. 141-142°C

% yield = 55.6

Analysis: Calc.(%): C = 63.16, H = 7.89, N = 18.42. Found (%): C = 63.34, H = 7.61, N = 18.57

MS (m/z): M/e 154 (M^+), 137, 109, 96, 82

(±) 2-Tropinone Oxime Methiodide (51)

The above oxime (50, 0.11 g) was dissolved in 20 ml of dry chloroform and stirred at room temperature with an excess of methyl iodide. The product separated out immediately. Filtration gave a white solid weighing 0.180 g.

mp. 207-211°C (decomposition)

% yield = 87

Analysis: % Calc., C = 36.73, H = 5.10, N = 9.52, I = 43.20. Found: % C = 36.76, H = 5.21, N = 9.24, I = 43.56

MS (m/z): M/e 154, 142, 137, 128

Synthesis of 2α-Hydroxy 3-Oximino Tropane Methiodide (55)

2α-Hydroxy 3-Tropinone Dimethyl Acetal (52)

The ketone 3-tropinone (5.0 g, 0.036 mole) in 30 ml MeOH was added dropwise to a stirring solution of KOH, 6.05 g in 75 ml MeOH.[13] After 10 minutes, iodosobenzene diacetate (13.14 g, 0.0395 mole) was added in small portions. The mixture was allowed to stir overnight at room temperature. After removal of the solvent at reduced pressure, the reddish residue was taken up in 75 ml water and washed with hexane to remove iodobenzene. The aqueous solution was then extracted six times with chloroform. The organic layers were combined, dried and evaporated to dryness. The oil was swirled with hexane and cooled to allow crystallization of acetal (52). Filtration gave 2.47 g colorless crystals.

mp. 85-86°C

% yield = 34

NMR($CDCl_3$)δ: 3.24 (3H, -OMe), 3.29 (3H, -OMe), 3.88-3.90 (1H)

MS(m/z): M/e 201 (M^+), 170 (m-31), 97, 96, 82

2α-Hydroxy 3-Tropinone (52)

The above acetal (52, 2.0 g) was treated with 45 ml of 1N HCl at room temperature for one hour. The acidic solution was neutralized carefully with sodium bicarbonate and extracted repeatedly with chloroform. The organic layers were combined, dried with magnesium sulfate, and evaporated to give 1.24 g of crude crystalline product. The product was recrystallized from hexane to give white needles. NOE experiments were performed on the 400 MHz spectrometer using a

$CDCl_3$ solution of (52) purged with N_2 to exclude oxygen.

m.p. 65-66°C.

IR($CDCl_3$)cm^{-1}: 3505 (-OH), 1715 (C=O)

NMR($CDCl_3$)δ: 2.52 (m, 3H, N-CH_3), 4.26 (m, 1H, C_2-H)

MS (m/z): M/e 155 (M^+), 125, 124, 112, 98, 96, 82

2α-Hydroxy 3-Oximino Tropane (54)

The recrystallized ketone (52, 1.0 g, 0.006 mole) was dissolved in 30 ml of absolute ethanol and stirred with one equivalent (0.45 g) of hydroxylamine hydrochloride. The isolated hydrochloride was dissolved in 25 ml water and neutralized with sodium bicarbonate. Extraction with methylene chloride gave 0.74 g of the oxime (54).

m.p. 165-169°C

% yield = 74

IR(Nujol)cm^{-1}: no C=O peak

2α-Hydroxy 3-Oximino Tropane Methiodide (55)

The hydroxy oxime (54 ,0.50 g, 0.003 mole) was dissolved in dry methylene chloride and treated with an excess of MeI. The product weighed 0.86 g, based on the oxime.

m.p. 189-192°C

% yield = 92

NMR(D_2O)δ: 3.34, 3.2 (2N-Me), 5.05

Analysis: Calc. (%): C = 34.61, H = 5.45, N = 8.97, I = 40.70. Found (%): C = 34.42, H = 5.49, N = 8.91, I = 40.52

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APPENDIX

10. PUBLICATIONS FROM THE SECOND YEAR

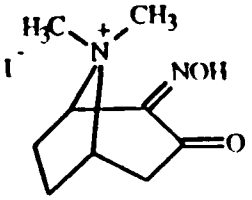
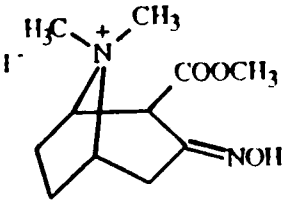
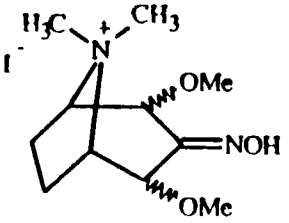
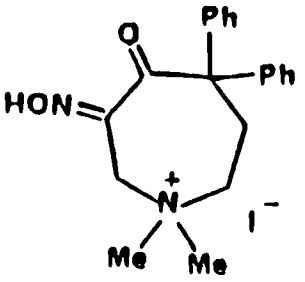
1. "Carbon-carbon Bond Formation Using Hypervalent Iodine Under Lewis Acid Conditions: 1,4-Diarylbutane-1,4-diones," R.M. Moriarty, O. Prakash and M.P. Duncan, *J. Chem. Soc. Chem. Commun.*, 420 (1985).
2. "Use of Hypervalent Iodine Oxidation for the C(3)-Hydroxylation of Chromone, Flavone and α-Napthoflavone," R. M. Moriarty, O. Prakash and H.A. Musallam, *J. Heterocyclic Chem.*, **22**, 583 (1985).
3. "Hypervalent Iodine Oxidation of Enol Silyl Ethers Using Boron Trifluoride Etherate. A Direct Route to Aryl α-Hydroxymethyl Ketones," R.M. Morairty, O. Prakash and M.P. Duncan, *Synthesis*, 943 (1985).
4. "Synthesis of a-Hydroxydimethylacetals from Nitrogen Heterocyclic Ketones Using Hypervalent Iodine Oxiation," R. M. Moriarty, O. Prakash and C.T. Thatchet, *Heterocycles*, **23**, 633 (1985).
5. "Solvohyperiodination. A Comparison with Solvothallation,," R.M. Moriarty, J.S. Khosrowshahi and O. Prakash, *Tetrahedron Letters*, **26**, 2961 (1985).
6. "Hypervalent Iodine Oxidation: Synthesis of Spin-labelled 1-Oxyl-2,2,6,6-tetramethylpiperidine Derivatives," R.M. Moriarty, I. Prakash and R. Penmasta, *J. Heterocyclic Chem.*, **22**, 1581 (1985).
7. "Possible Role of Lewis Acid Catalysis in the Oxidation of Alkenes and α,β-Unsaturated Ketones Using Bleomycin-Zn(II) and Bleomycin-Fe(III)-iodosylbenzene in Aqueous Methanol," R. M. Moriarty, R. Penmasta and I. Prakash, *Tetrahedron Lett.* **26**, 4699 (1985).
8. "Hypervalent Iodine Oxidation of Flavanols Using [Hydroxy(tosyloxy)iodo]benzene in Methanol," R.M. Moriarty, O. Prakash H.A. Musallam and V.K. Mahesh, *Heterocycles*, **24**, 1641 (1986).
9. "Oxidative Cleavage of Ketooximes with Iodosobenzene Diacetate," R.M. Moriarty, O. Prakash and P.R. Vavilikolanu, *Syn. Comm.*, **16**, 1247 (1986).
10. "Hypervalent Iodine Oxidation of 1-Trimethylsilyloxy-1-(2'-trimetnylsilyloxyphenyl)-ethene. Synthesis of 3-Coumaranone and 2,2'-Dihydroxyacetophenone," R.M. Moriarty, O. Prakash and M.P. Duncan, *Syn. Comm.*, **16**, 1239 (1986).

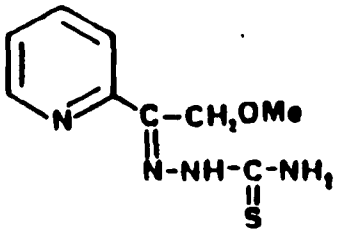
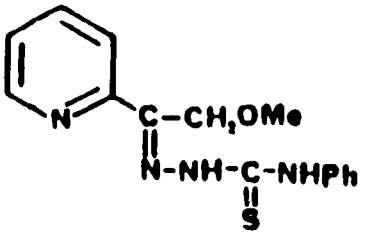
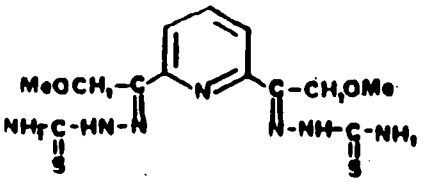
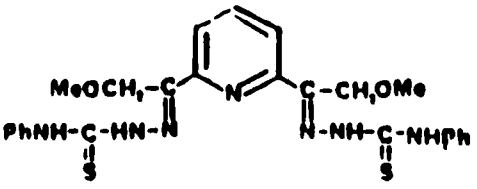
11. PAPERS PRESENTED at *ACS* MEETINGS

1. "Tropane Oximes: Synthesis and Reactivation of Phosphorylated Acetylcholinesterase," R.M. Moriarty, P.R. Vavilikolanu, O. Prakash, T. Dougherty and H.A. Musallam.
2. "Phencyclidine Oximes: Synthesis of 1-(1-Phenylcyclohexyl)-4-Piperidoner and 4-(1- Piperidin yl)-4-Phenylcyclohexanone Oxime Methiodides as Acetylcholinesterase Reactivators," R.M. Moriarty, P.R. Vavilikolanu, P. Farid, T. Dougherty and O. Prakash.
3. "Oxidative Cleavage of Oximes with Iodosobenzene Diacetate," R.M. Moriarty, O. Prakash and P.R. Vaviliokanu.

12. COMPOUNDS SUBMITTED TO *WRAMRDC*

Samples Submitted for Test and Evaluation

Code No.	Compound Structure	Compound Name	Quantity
PRV-188 BL-24450		2-Oximino Tropan-3-one hydrochloride	2.0g
PRV-151 WR-255127 IDC# 483 BL-13395		2-Carbomethoxy 3-oximino 3-oximino tropane methiodide	2.0g
OP-735 WR-255126 IDC# 484 BL-13402		2,4-Dimethoxy-3-oximino-tropane methiodide	2.0g
PRV-163 BL-25883		1-Methyl-3-oximino-5,5-diphenyl azacycloheptan-4-one methiodide	2.01g

Code No.	Compound Structure	Compound Name	Quantity
OP-700 WR-254750 BL-09846		2-(Methoxymethylcarbonyl pyridine thiosemicarbazone	1.95g
OP-688 WR-254749 BL-09837		2-(Methoxymethylcarbonyl) pyridine 4′-phenylthiosemi-carbazone	2.0g
OP-661 WR-254748 BL09828		2,6-Bis(Methoxymethyl-carbonyl)pyridine bis-thio-semicarbazone	2.0g
OP-705 WR-254751 BL-09855		2,6-Bis(Methoxymethyl-carbonyl)pyridine bis-4′-phenyl-thiosemicarbazide	2.0g